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Radiobiological Risk Estimates for Space Flight Based on Long-Term Studies in Proton-Irradiated Primates

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Between 1963 and 1969, 301 young rhesus monkeys were exposed to low and intermediate doses of X-rays, protons or electrons to simulate space radiation hazards, 57 control animals were incorporated in the experimental design, and both sexes were represented. The subjects have been followed for nearly 30 years, and major findings of the study include: 1) highly significant incidence of glioblastoma mutliforme (high-grade astrocytoma) in male animals exposed to 55-MeV protons; 2) highly significant incidence of severe endometriosis in female subjects exposed to different radiation energies and doses; 3) development of significant late lenticular opacifications (cataracts) in monkeys 20+ years following exposures to low and intermediate doses of protons. As the animals age, abundant data are expected to provide additional insights into the late stochastic (probabilistic) and deterministic effects induced in primates by exposures to low and intermediate doses of particulate radiations. Refined space radiobiological risk estimates, based on a long-lived primate model closely resembling the human in many of its responses to ionizing radiations, will enable scientists and engineers to design spacecraft and associated hardware to maximize the short- and long-term safety of personnel participating in lengthy space missions.

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ABSTRACT

Between 1963 and 1969, 301 young rhesus monkeys were exposed to low and intermediate doses of X-rays, protons or electrons to simulate space radiation hazards; 57 control animals were incorporated in the experimental design, and both sexes were represented. The subjects have been followed for nearly 30 years, and major findings of the study include: 1) highly significant incidence of glioblastoma multiforme (high-grade astrocytoma) in male animals exposed to 55-MeV protons; 2) highly significant incidence of severe endometriosis in female subjects exposed to different radiation energies and doses; 3) development of significant late lenticular opacifications (cataracts) in monkeys 20+ years following exposures to low and intermediate doses of protons. As the animals age, abundant data are expected to provide additional insights into the late stochastic (probabilistic) and deterministic effects induced in primates by exposures to low and intermediate doses of particulate radiations. Refined space radiobiological risk estimates, based on a long-lived primate model closely resembling the human in many of its responses to ionizing radiations, will enable scientists and engineers to design spacecraft and associated hardware to maximize the short- and long-term safety of personnel participating in lengthy space missions.

INTRODUCTION

Outside the protection of the magnetosphere, humans and electronic equipment will be vulnerable to the effects of charged particles. Shielding against most protons will be accomplished by execution of spacecraft designs based on studies not only of the space environment(s) to be met but also on research projects devised to determine radiological health risk estimates for humans existing in the environment(s). Some risk estimates can be determined from very limited extant human data bases, but the bulk of the data from which relevant risk factors must be derived will come from experiments on animals exposed to relativistic particulate radiations.

The National Council on Radiation Protection and Measurements (NCRP) published a report in 1989 which summarized information on available data bases, both physical and biological, available at that time (1). An ongoing project with non-human primates, initiated in 1963 by the United States Air Force (USAF) and the National Aeronautics and Space Administration (NASA) continues to provide data on probabilistic and deterministic radiation effects (caused primarily by protons). A series of articles on the Delayed Effects Colony (DEC) of rhesus monkeys, which currently is being supported by the USAF and NASA, summarizes information known about the DEC through 1989 (2-7). It is the purpose of this "mini-review" to emphasize the most significant results, including some of the recent ones, from this project.

METHODOLOGY

Rhesus monkeys (estimated age: 2-4 years) were exposed to various energies of protons (32, 55, 138, 400 or 2300 MeV; 10 and 110 MeV in a ratio of 10:1) to simulate irradiation from solar particle events. Details of the treatments are reviewed by Hardy (3), but it should suffice to say here that protons of energies ranging from 10-55 MeV were partly penetrating (sparing the core of the body and center of the brain) while the higher energies penetrated the bodies fully. Further information on doses received by the irradiated monkeys can be found in the article by

Leavitt (4). Reëvaluation of the dosimetry, especially those doses received by the brain, was necessitated by the high incidence of glioblastoma multiforme (high-grade astrocytoma, or HGA) found in a significant number of the male primates which received 55-MeV protons (3, 4). The cancer incidences were reviewed recently by Wood (5).

Endometriosis was found at necropsy in some of the females early in the post-irradiation time frame, and about 10 years ago, it was decided to examine the animals for that disease before it became fatal (6). A number of animals were diagnosed with endometriosis, and hysterectomies were performed on those individuals. Details of the procedures used may be found in the article by Fanton and Golden (6).

The primates were evaluated for cataracts at various post-irradiation times, but it was not until 1985 that systematic cataract scoring was initiated by Lett et al. (7). A subjective scoring system that had been established using rabbits exposed to low- or high-LET radiations was applied successfully to the monkeys, and details of that scoring system may be found in the article by Keng et al. (8). In essence, the scoring system ranges from zero (completely clear "normal" lens) to 5 (totally opaque lens through which light cannot pass) with gradations between 0 and 5 as the radiogenic cataracts develop (8).

RESULTS AND DISCUSSION

RADIOGENIC TUMORS - While tumor induction is a well-known result of exposure to ionizing radiations, the high incidence of glioblastoma multiforme (or high-grade astrocytoma = HGA) in male monkeys exposed to 55-MeV protons was a remarkable finding in the long-term study of proton-irradiated primates (5). HGA is a relatively rare tumor, and its incidence among humans is higher in males than in females. The occurrence of significant numbers of HGA in the proton-irradiated primates is significant for at least 3 reasons.

1) Development of HGA in the primates is a function of the manner in which protons, and other relativistic particles, deposit energy in mammalian tissues or equivalent materials. While doses of sparsely-ionizing radiations, such as X-rays, are attenuated as the photons pass through tissue-equivalent materials, doses of densely-ionizing radiations, such as relativistic protons, actually can be higher within a material than they are on the surface depending on the energy of the particles. For this reason, the 55-MeV proton-irradiated primates received doses to parts of their brains that in some instances were >300% higher than were measured surface doses to the subjects. Despite the "hot spots" that occurred in the brains of individuals from the 55-MeV group, much of the remainder of those animals' body volume remained unexposed to the protons because the penetration of 55-MeV protons was only 2.5 cm. For this reason, animals survived long enough to develop brain tumors in the areas of the "hot spots;" the likelihood of such tumors developing in subjects exposed whole-body either to sparsely-ionizing or fully penetrating densely-ionizing radiations is very low because other radiation damage would have preceded the development of HGA in most instances. The dosimetry data have been reviewed by Hardy (3) and Leavitt (4); details of tumor incidence for individual animals have been reviewed by Wood (5), and radiogenic HGAs, both in humans and primates, have been discussed by Dalrymple et al (9). Depth-dose depositions by protons ranging in energy from 32-400 MeV are illustrated by Conklin and Hagan in biological dosimetric terms using early data from the proton-irradiated monkey colony (10).

2) The occurrence of so many HGAs in the 55-MeV proton-irradiated subjects is important because, although the biological effectiveness of protons, relative to standard X-rays, may be relatively low overall, nonetheless the way in which proton energies are deposited in unit density materials resulted in an effect which might not have been seen had conventional sparsely-ionizing radiations been used for the experiments. Thus, while radiobiological data from protons may be applied to risk estimates for ionizing radiations in general, the unique radiobiological properties of densely-ionizing particulate radiations must be studied as well. Risk estimates for astronauts who might be exposed to protons in the trapped radiation belts or from solar particle events as well as for the normal tissues of radiotherapy patients undergoing proton and other particulate radiation therapies must be determined from experiments performed using accelerators designed specifically to produce biologically relevant particles for the environments of concern. Otherwise, serious complications from exposure to these unique but not insignificant environmental and therapeutic particles might be missed.

3) The value of experimental non-human primates must be emphasized in the context of proton-induced HGA. The data base on radiogenic HGA in humans is small, and all known human HGAs of this type were induced by sparsely-ionizing radiations (9). One reason for the appearance of the HGAs in the proton-irradiated primates is that, despite their small size relative to humans, rhesus monkeys are large enough so that numerous critical tissues were spared exposure during the experimental irradiations (see above). Not only could these results not have been obtained from the known human data base (see above), but also they could not have been obtained from experimental rodents, due to their small volumes relative to the patterns of energy depositions that occurred. Thus, for the brain tumor results alone, it was essential that an animal model larger than the standard laboratory rodent was used. Furthermore, the use of a non-human primate gives us more confidence that our radiation risk estimates based on the model will be accurate.

As of May 1993, the survivors of the original experimental groups include 14/57 (24%) control and 27/301 (9%) irradiated animals. Recently, the tumors seen most often at necropsy have been intestinal adenocarcinomas both in control and irradiated subjects. Statistical analyses of the current findings are under way, and first impressions indicate that most of what we are seeing now as causes of death are age-related phenomena.

RADIOGENIC ENDOMETRIOSIS - The high incidence of endometriosis in irradiated female subjects (6) was an unexpected finding with several sobering implications. Since we cannot go into great detail here, we will cover only a few points and refer the reader to reference (6). Briefly, "Endometriosis is the ectopic growth of uterine endometrium in locations outside the uterine borders. It is a common disease in women, occurring in up to 10% of the female population, and in 25-40% of infertile women. Endometriosis occurs spontaneously only in menstruating species, and in nonhuman primates the similarity with the human syndrome is considerable." (6). Unchecked either in humans or monkeys, the disease can interfere not only with reproduction but also with, e.g., processes associated with the gastrointestinal tract and other systems; the damage is caused by adhesions as the ectopic endometrium attaches to inappropriate tissues.

Since not all irradiated female monkeys developed endometriosis (26% of the control females developed the disease while 53% of all irradiated females presented with endometriosis), it may be considered, as is radiation carcinogenesis, a stochastic or probabilistic consequence of radiation exposure. The mechanisms of its induction are not fully understood at this time, but the development of the disease in irradiated primates has sparked renewed interest in the disease as an environmentally-induced phenomenon (see below). Some implications of results in females from the Delayed Effects Colony are enumerated below.

1) Women of reproductive age who elect to become astronauts should consider the possibility that space radiation exposure(s) might compromise their future reproductive abilities. It is clear that more research in this area is necessary, but the nonhuman primate model has provided data which are very important for determining radiation risk estimates specifically for females.

2) As a result of the article on radiogenic endometriosis published by Fanton and Golden (6), other research groups using primates for toxicological studies were induced to reëxamine some data from macaques exposed to various environmental toxins. It seems there were reports of possible chemical induction of endometriosis which had not yet been published in the open literature. The compounds to which female macaques had been exposed included a) TCDD (2,3,&,8-tetrachlorodibenzo-p-dioxin), b) polychlorinated biphenyls (PCB's) and c) mycotoxin deoxynivalenol (DON). Following exposure to any of these three chemical agents, endometriosis was induced and/or exacerbated in experimental subjects. In 1992, 17 female monkeys previously exposed to dioxin were "spared" from being assigned to unrelated experimental protocols, and will be observed for possible development of endometriosis for at least 3 more years. The information on the possible links between environmental chemicals and endometriosis was provided by M. Ballweg as a personal communication.

3) Once again, the necessity not only for experimental animal models, but also for experimental nonhuman primate models is emphasized by these sets of results. Only species which exhibit menstrual cyclicity develop endometriosis. Thus, rodents, which undergo estrous rather than menstrual cycles would not have developed endometriosis following exposures either to ionizing radiations or environmental toxins, and an effect extremely important to the health of women of reproductive age would have been missed completely.

RADIOGENIC CHROMOSOME ABERRATIONS - It is known that ionizing radiations produce chromosome aberrations in the cells of exposed animals. Until very recently, the detection of such aberrations, especially the translocations which can persist for years following exposure, was a tedious and labor-intensive task. The development of molecular "probes" for all the human chromosomes has enabled scientists to utilize a technique called fluorescence in situ hybridization (FISH) to highlight changes in the chromosomes which can be detected and quantified relatively easily. Although application of the human probes to cells from some non-human primates (such as selected new-world species) has not produced ideal results, it turns out that the human probes may be applied to the chromosomes of macaques (including rhesus monkeys), and persistent translocations in cells from irradiated monkeys can be quantified (11). There are at least 2 implications of these results.

1) Because the doses received by the primates in the Delayed Effects Colony are known quite accurately, analyses of cells from these subjects by the FISH technique, now under way, should provide scientists with dose response curves which will be more accurate than curves derived from human victims of radiation accidents, the doses for whom are only estimates. This data base will, in turn, be applicable to patients exposed in earlier accidents and in future environmental crises of various kinds, including accidents on earth suffered by, e.g., reactor personnel, and solar particle events to which astronauts might be subjected.

2) The ability of scientists to "paint" macaque chromosomes with molecular probes designed for human chromosomes further strengthens our ability to extrapolate experimental data of many types from selected non-human primates to humans. The close

evolutionary ties between macaques and humans are verified by the similarities between chromosomal sequences in the two primates. Once again, the advantage of the nonhuman primate model, when compared to standard rodent models, for which entirely different chromosome probes must be developed, is validated.

RADIOGENIC CATARACTS - Cataracts induced by ionizing radiations are deterministic effects in that, while not all exposed individuals will necessarily develop clinically significant cataracts, they will present with lenticular opacifications over and above those which would appear naturally with age. It is important to determine the kinetics of cataractogenesis following exposures of relevant animal models to ionizing radiations of different characteristics, and this has been accomplished to a great extent throughout the life span of New Zealand white rabbits exposed both to sparsely- and densely-ionizing radiations (e.g., 7,8,12,13). In primates comprising the Delayed Effects Colony, radiogenic cataracts have been followed since 1985, i.e., from 20-27 years following irradiation with protons. In addition, the eyes of some monkeys exposed to intermediate and high doses of sparsely-ionizing radiations and "rescued" with bone-marrow transplants at the Radiobiological Institute, TNO, Rijswijk, The Netherlands, have been examined, and selected data from both studies are shown in Figure 1 (see also 14).

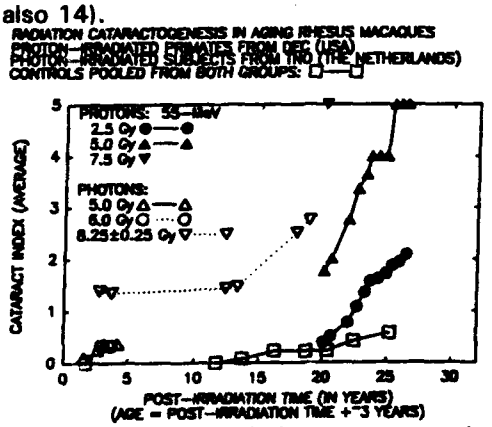

Fig. 1. Average cataract index versus post-irradiation time for two groups of rhesus monkeys exposed to ionizing radiations (protons or photons). Symbol key appears in the figure. Reproduced with permission of the authors of reference (14).

It should be noted that with the scoring system described in (8), concern about an individual's vision need not arise until the cataract index rises above 1, and surgery would be indicated, for a human patient, after a cataract level between 1.5 and 2 were reached. Some points to heed in Fig. 1 are stressed here. The data from the Delayed Effects Colony dates only from 20 years post-irradiation. Cataracts were recorded prior to that time, but they were not quantified as they have been since 1985. The TNO data serve to fill in some of the blanks left by the absence of early quantitation of the DEC data. Also, it may be noted that almost 5 years after exposure, the TNO subjects exposed to 5 or 6 Gy exhibit only low levels of lenticular opacification. Although the measurements are not directly superimposable, due to the different qualities of radiation applied to the subjects, the combined data are suggestive, and when the project is completed, correction factors will be derived and extrapolation among experimental groups, as well as among the various animal models in which radiogenic cataracts have been studied, will be accomplished.

As stated above for radiogenic endpoints including cancer, endometriosis and chromosome aberrations, many of the data obtained from rhesus monkeys examined for cataractogenesis could not have been secured from short-lived rodent species. Most rodent models show high levels of lenticular opacification among controls starting as early as one year of age. Such high "natural" levels of cataract can confound the interpretation of late radiogenic cataracts following relatively low doses of ionizing radiations.

Some efforts have been initiated in the area of cataract data extrapolation already. The lenses of human radiotherapy patients exposed to helium ions are being examined now, and quantitation of changes in those lenses should be such that extrapolation of animal to human data will result (15). In addition, some animal cataract data have been utilized by modelers of the space radiation environment (16). It is our ultimate hope that all the data from long-term studies of radiation effects in animals and humans will be folded into environmental models for space and other environments.

SUMMARY AND CONCLUSIONS

Only some of the high points of our studies in nonhuman primates have been discussed in this presentation. It should be clear, however, that for proper risk estimates to be made for future space travelers, several areas of radiobiological research must be emphasized.

1) Data bases on irradiated animals and humans, including those exposed to sparsely-ionizing radiations, (e.g. the X-irradiated TNO monkeys discussed here and in reference 14; the survivors of the Atomic bombs at Hiroshima and Nagasaki; the survivors of the accident at Chernobyl; radiotherapy patients) must be utilized for space radiation risk estimates. Nonetheless, as the proton-induced brain tumors in monkeys make clear, the radiobiological data bases for effects of particulate radiations also must be expanded. Hence there is a need for accelerator facilities appropriate for the relevant research.

2) The development of endometriosis in significant numbers of irradiated female primates is a phenomenon which could not have been seen in rodent models or in cell cultures. Thus, it is plain that there is a need for continued animal experimentation, including

work on nonhuman primates, not only for space radiation risk estimates but also for terrestrial environmental risk estimates of all kinds, including those for radiation and toxic chemicals. This will be especially important for some women's health issues, e.g. endometriosis.

3) We cannot emphasize strongly enough the need for studies of true radiobiological late effects in whole organisms. Astronauts are unlikely to be exposed to lethal doses of radiation during, e.g. a mission to Mars, due to the communications to them of solar activity, etc., that will undoubtedly be routine. It is upon their return to the Earth and later that stochastic and deterministic effects will be expressed in these individuals. For this reason it is imperative that late effects of ionizing radiations be studied in as great depth as possible for the most accurate calculations of radiation risk estimates to be realized.

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